The CenterWatch Monthly

February 2018 A CenterWatch Feature Article Reprint Volume 25, Issue 02

Rare Disease Recruitment Models Evolving

The Impact of Real-World Outcomes and Trial Design in the Rare Disease Arena

By Sony Salzman

The FDA has released a flurry of guidance that signals its growing willingness to accept flexible study designs and real-world evidence in drug submissions for rare disease trials — welcome news for study sponsors because it opens the door for new technology and new models to recruit and retain rare disease patients.

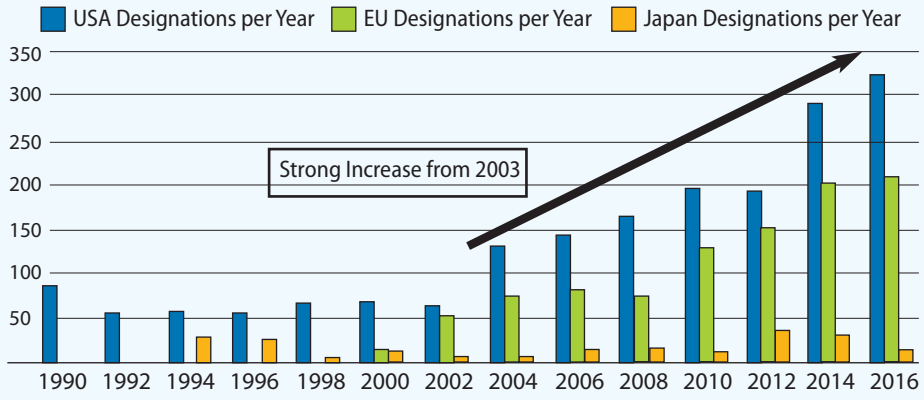
Regardless of shifting policies in Washington, D.C., sponsors, research groups and patient advocates are staying creative as they explore ways technology can be used to overcome patient recruitment and retention obstacles.

Study sponsors have traditionally relied on advocacy groups and a handful of specialist research centers to recruit patients for rare disease clinical trials. Now, however, drug companies and contract research organizations (CROs) are turning to big data and predictive algorithms to scan the electronic medical record (EMR) for people who might be eligible for these studies.

Recruitment Challenges, Meet Big Data

Modern efforts to improve recruitment of rare disease trials fall into three main categories. The first is associated with the birth of online networks and social media — tools immediately adopted by advocacy groups and pharma sponsors alike to identify a global pool of patients.

USA EU & Japan Designations per Year



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Second, some research groups have begun to leverage big data by scanning EMRs for high-density clusters of patients. Finally, some researchers are engaged in more nascent efforts to build sophisticated algorithms that can use EMR data to identify rare disease patients who have not yet been formally diagnosed.

The rise of social media has significantly changed recruitment strategies for rare disease clinical trials, said Tom Ruane, global head, Patient Recruitment, PAREXEL. "Today, patients facing rare diseases and their families are extremely active online, due to their personal desperation and lack of resources," Ruane said. "Social media has allowed patients with rare diseases to learn about ongoing trials all over the world and new treatments in development that they may not have heard about otherwise."

While social media has offered a perfect vehicle for patients to advocate for themselves, the widespread adoption of electronically-stored medical records has helped study sponsors dramatically improve the traditional process of site selection for rare disease trials. For example, EMR systems can now be programmed to offer "alerts" to physicians when patients might be eligible for clinical trials, a feature that has improved prospective recruitment in rare disease research, according to a study in the Journal of the American Medical Informatics Association.

Companies with access to large EMR databases can also use natural language processing — a powerful method of reading free-form entries in a non-standardized EMR — to screen for sites with clusters of rare disease patients living nearby, according to global health research network TriNetX.

In addition to merely querying EMR data, some early efforts are underway to build predictive models that can scan EMRs to not only identify, but also diagnose, patients with rare diseases. The purpose of these predictive models is "to identify high probability patients," said Richard Gliklich M.D., founder and chief executive officer, OM1.

Too often, "you have a patient that may go five years without a diagnosis" because

rare disease symptoms are often misdiagnosed or just plain missed, said Gliklich. Predictive analytics "increases the number of patients that are potentially available" to enroll in clinical research.

Although it's early days for predictive analytics in rare disease trials, Gliklich's company is already working with clients that are interested in testing the feasibility of these models. Other companies such as Vencore offer solutions for patient discovery using analytics.

According to a recent McKinsey report, machine learning can be leveraged to not only identify candidates for clinical trials by targeting specific populations, but also be used to find the best sample size and optimize recruitment at different sites.

Outside the EMR arena, other modern approaches to improving recruitment in rare disease trials borrow from the playbook of companies like Google and Facebook, which have perfected the science of delivering precise, personalized advertisements.

In 2017, the NIH-funded Rare Diseases Clinical Research Network announced results of a study that compared direct recruitment and via online marketing to the traditional approach of enrolling patients through centers of excellence, focusing on the rare disease granulomatosis with polyangiitis.

Although the online approach was not as successful as the traditional approach (respectively enrolling 10 and 49 patients), the researchers noted a major handicap was in the ability to get community physicians to facilitate the enrollment process. Overcoming that hurdle might open the door to direct-to-patient recruitment, especially because patients recruited online were "capable of understanding and correctly appraising whether or not they met the eligibility criteria," the authors noted.

Patient-Centricity For Outcomes and Retention

In rare disease trials, recruitment is only half the battle. Because patients are so geographically dispersed, many find it challenging to travel to a central research hub. For that reason, rare disease trials have become a key pillar of the virtual trial movement, which seeks to transform trial participation from a burden into an opportunity for patients.

"Remote studies are another area where innovation is redefining the clinical trial process," said Ruane. "Through technology such as wearables, telemedicine and home infusion services, patients can now participate in studies that are taking place at a center thousands of miles away from them."

Patients within the rare disease community are unique because they are typically fierce advocates on behalf of their own health. An essential retention strategy in rare disease trials is to ensure that patients feel that their participation is empowering and educational.

In addition, because many rare disease patients are children, their caregivers, often parents, are responsible for collecting primary and secondary endpoints in a clinical trial. That means rare disease trials require additional infrastructure so that caregivers can be trained on how to properly and objectively collect those endpoints across cultural settings, said Susan Dallabrida, VP, Clinical Science & Consulting, ERT.

"The stakes are so high. The caregivers need to administer this instrument properly. One [issue] has to do with the instrument itself, but the second is the caregiver is in an emotionally connected role," said Dallabrida.

According to Dallabrida, the FDA now commonly asks companies to prove that they have robust training materials in place so that caregivers understand the ins-and-outs of their role in the study and how to accurately report on the patient diary data.

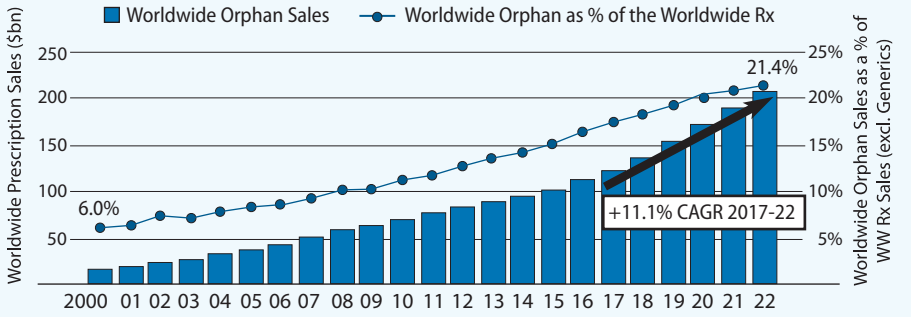
"There's a lot of data today that now shows that whether you're younger or older, people favor interactive media," said Dallabrida. Often, this educational component is done through an eCOA vendor, a CRO, an outside vendor or through an advocacy organization.

Advocacy groups "play an important role in simplifying the complex languages and processes of trials for patients," echoed Ruane. "Therefore, it's important for the industry to educate and inform patient advocacy groups in order to ensure we're meeting the needs of patients."

Recent FDA Actions Signal Flexibility

Over the past few years, the FDA has published several major guidance documents that expand the variety of accepted evidence for rare drug registration trials. In 2014, the FDA held a three-day meeting to explore new ways to encourage rare dis-

Wordwide Orphan Drug Sales & Share of Prescription Drug Market



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ease drug development, during which the agency discussed flexible endpoints such as patient-reported outcomes and surrogates that can be considered in registration trials. The following year, the FDA released draft guidance which outlined, in greater detail, appropriate ways to generate and collect patient reported outcomes in rare disease trials.

"This is still early days, but with the 21st Century Cure Act [of 2016], the FDA had stated that using real-world evidence can replace certain aspects of clinical trials," said Gliklich. "That is more likely to be the case in conditions where approvals are based on very limited data. So it seems that rare diseases may be an area that gets initially impacted by use of real world evidence."

In December 2017, the FDA released new draft guidance which proposed a new type of multi-arm, multi-company study design for Gaucher disease, a rare pediatric disease. Although announced as a "proposal only," the FDA also noted that the "principles underlying the proposal may be extended to other areas of drug development in rare diseases." An FDA spokesperson added, "Sponsors developing drugs intended for pediatric rare diseases should consult with the FDA on trial designs and use of real-world evidence."

Judith Ng-Cashin, M.D., chief scientific officer, Clinical Solutions, Syneos Health, said, "The recent guidance focuses on promoting a collaborative approach for clinical trial design and execution between multiple sponsors, patient groups and investigators. Specifically, it encourages consideration of an 'umbrella' type study design in which multiple potential therapies (from potentially multiple sponsors) are included as separate treatment arms in the same trial."

This proposed study design would have the additional benefit of slashing the risk that patients would receive a placebo — something that dissuades patients with rare, life-threatening illnesses from participating in trials.

"While real world evidence is not specifically mentioned, the requirement for long term safety and efficacy monitoring beyond the formal clinical trial is expected," said Ng-Cashin. "The FDA recommends that the data collected within these long-term registries also be harmonized across sponsor, treatment, and regulatory authorities — even including data on children born to treated mothers."

Using real-world data is a good option for rare disease research, said Gliklich. "Most studies for rare disease have been based on observational data or very small trials by nature," said Gliklich, so approval could be granted with "enough evidence that a treatment is working in the wild."

Broadly, the FDA will need to increasingly employ more diverse types of clinical evidence, including adaptive statistical approaches used across related disease variants, in-vitro testing, when appropriate, and even in-silica modeling in extremely small patient populations, said Karen Kaucic, M.D., senior vice president, global head of Early Development and PPD's Rare Disease and Pediatric Center of Excellence.

"As 'subgroups of subgroups' of diseases are identified, regulatory bodies will be increasingly faced with the challenge of approving therapies based on limited clinical evidence," said Kaucic.

"In a recent example, the label for ivacaftor, a gene therapy for cystic fibrosis, was expanded from 10 to 33 mutations based not on additional clinical data but on the results of in vitro data, paving the way for other regulatory approvals supported by laboratory rather than clinical trial data," Kaucic said.

Dallabrida said, "The patient-reported outcome, or the observer reported outcome, is often either the primary endpoint or a key secondary endpoint in rare disease."

For rare diseases, "the value of the observational data is high, and the downside of using a placebo in a patient you could otherwise help is pretty big. That's why I think the ethical imperative is going to drive more use of real-world evidence," said Gliklich.

Rare Disease Informs Precision Medicine

Moving forward, experts expect that the lessons learned from rare disease research will be applied in the growing precision medicine movement, as even common diseases such as diabetes are isolated into smaller and smaller disease categories based on genetic and environmental differences in each patient. This, in turn, will shape the way patients are recruited across the entire clinical research enterprise.

"The move toward precision medicine is going to require a paradigm shift within the pharmaceutical ecosystem to address how evidence to support regulatory approvals is generated and how patients are identified and enrolled in clinical trials," said Kaucic.

As part of this paradigm shift, study sponsors are exploring the way modern technology can help cast a wider net for rare disease recruitment and keep patients engaged, and how to standardize trial endpoints that are meaningful for patients and relevant to regulators.

Sony Salzman is a freelance journalist reporting on healthcare and medicine. She earned her Master's degree from Boston University's Science Journalism program, and has won multiple awards for narrative writing and radio journalism. She can be reached at sonysalz@gmail.com, or on Twitter @sonysalz.